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(54) Title: POTENTIATION OF NMDA ANTAGONISTS

(57) Abstract

The present invention is directed to a method for potentiating the therapeutic effects of selected NMDA antagonists

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POTENTIATION OF NMDA ANTAGONISTS

The present invention is directed to a method for potentiating the therapeutic effects of a group of
5 excitatory amino acid antagonists. Another aspect of the invention is directed to new pharmaceutical compositions useful for the treatment of conditions associated with excessive excitatory amino acid activity.

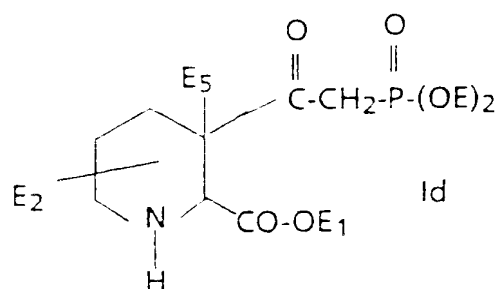
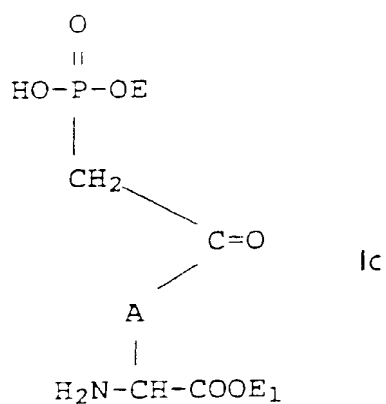
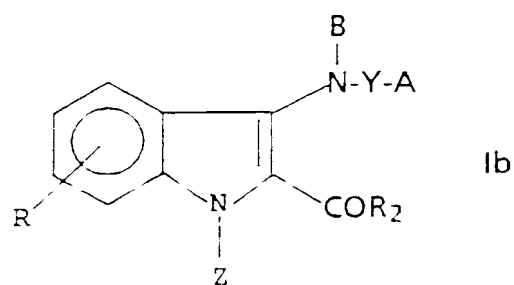
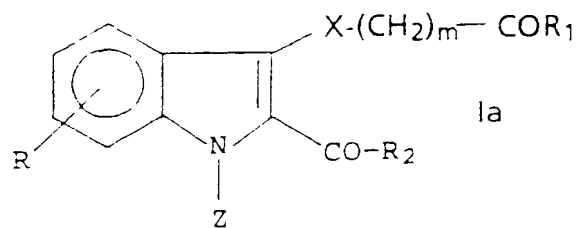
10 In accordance with the present invention, it has been discovered that probenecid will potentiate the activity of the following excitatory amino acid antagonists:

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- a) in the compounds of Formula Ia, X is represented by a linear C₁₋₄ alkylene, or S; m is an integer from 1-4; Z is represented by H, C₁₋₄ alkyl, phenyl, substituted phenyl, or an alkylphenyl substituent in which the phenyl ring may be optionally substituted; R is represented by hydrogen, halogen, C₁₋₄ alkyl, C₁₋₄ alkoxy, CF₃, OCF₃, OH, NO₂, or CN; R₁ and R₂ are each independently represented by -OH, -OR₃, -NR₄R₅, -OCH₂OR₃, or -O-(CH₂)_n-NR₆R₇, in which n is an integer from 1-4; R₃ is represented by C₁₋₄ alkyl, phenyl, substituted phenyl or an alkylphenyl substituent in which the phenyl ring may be optionally substituted; R₄ and R₅ are each independently represented by hydrogen or a C₁₋₄ alkyl; R₆ and R₇ are each independently represented by hydrogen or a C₁₋₄ alkyl, or R₆ and R₇ together with the adjacent nitrogen atom form a piperidino, morpholino, or pyrrolidino group with the proviso that if X is a C₁₋₄ alkylene, then m is 0;
- b) in the compounds of Formula Ib, R, Z, and R₂ are as above, B is represented by hydrogen, C_{1-C4} alkyl, optionally substituted alkylphenyl, or -CH₂-COR₂; Y is SO₂ or CO; and A is represented by phenyl, substituted phenyl, or C(O)D in which D is defined as R₂ above;
- c) in the compounds of Formula Ic, E is represented by hydrogen, C₁₋₄ alkyl, or -CF₃; A is represented by a methylene or a trimethylene bridging group; and E₁ is represented by hydrogen, C₁₋₄ alkyl, cycloalkyl, trialkylamino, alkylphenyl, phenyl, or substituted phenyl;
- d) in the compounds of Formula Id, E and E₁ are as above,

E₅ is represented by hydrogen, linear C₁-C₄ alkyl, or alkylphenyl; or a pharmaceutically acceptable salt of any of the compounds of Formulae Ia-d.

5 It has been discovered that probenecid will potentiate the therapeutic activity of the excitatory amino acid antagonists described by Formulae Ia-Id above (hereinafter the compounds). Thus the compounds will exhibit their therapeutic effects at lower doses and for longer periods in
10 patients who are concurrently receiving probenecid. The mechanism by which probenecid potentiates their effects is not fully understood, however it is believed that probenecid decreases the rate at which the compounds are removed from the central nervous system as well as decreasing their rate
15 of excretion by the kidneys. Probenecid increases the effective concentration of these compounds in both the CNS and in the systemic circulation.

As used in this application:

- 20 a) the terms "lower alkyl group and C₁-C₄ alkyl" refer to a branched or straight chained alkyl group containing from 1-4 carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, etc;
- 25 b) the terms "lower alkoxy group and C₁-C₄ alkoxy" refer to a straight or branched alkoxy group containing from 1-4 carbon atoms, such as methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, etc.;
- 30 c) the term "cycloalkyl" refers to a cyclohexyl or a cyclopentyl group;
- d) the term "substituted phenyl ring" refers to a phenyl (C₆H₅) which is substituted with up to 3 substituents, each substituent is independently selected from the
35 group consisting of halogens, C₁-C₄ alkyl, C₁-C₄ alkoxy,

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CF₃, OCF₃, OH, and CN. These substituents may be the same or different and may be located at any of the ortho, meta, or para positions;

5 e) the term "alkylphenyl substituent" refers to the following structure $-(CH_2)_m-C_6H_5$, in which m is an integer from 1-3. This phenyl ring may be substituted in the manner described immediately above;

10 h) the term "pharmaceutically acceptable addition salt" refers to either a pharmaceutically acceptable acid addition salt or a pharmaceutically acceptable basic addition salt;

15 i) the term "halogen" refers to a fluorine, bromine or chlorine atom;

20 j) the term "trialkylamine" refers to $-(CH_2)_n-N-\overset{\text{Alk}}{\underset{|}{\text{Alk}}}_1$ in which n is represented by an integer from 2-4 and Alk and Alk₁ are each independently represented by a C₁-C₄ alkyl; and

k) the term "cyclohexylmethyl" refers to $-CH_2-C_6H_{12}$.

25 The expression "pharmaceutically acceptable basic addition salts" is intended to apply to any non-toxic organic or inorganic basic addition salts of the compounds represented by Formulae Ia-d or any of its intermediates. Illustrative bases which form suitable salts include alkali
30 metal or alkaline-earth metal hydroxides such as sodium, potassium, calcium, magnesium, or barium hydroxides; ammonia, and aliphatic, alicyclic, or aromatic organic amines, including ethylamine, diethylamine, trimethylamine,

and picoline. Either the mono- or di-basic salts can be formed with those compounds.

The expression "pharmaceutically acceptable acid addition salts" is intended to apply to any non-toxic organic or inorganic acid addition salt of the base compounds represented by Formulae Ia-d or any of its intermediates. Illustrative inorganic acids which form suitable salts include hydrochloric, hydrobromic, sulphuric, and phosphoric acid and acid metal salts such as sodium monohydrogen orthophosphate, and potassium hydrogen sulfate. Illustrative organic acids which form suitable salts include the mono-, di-, and tricarboxylic acids. Illustrative of such acids are for example, acetic, glycolic, lactic, pyruvic, malonic, succinic, glutaric, fumaric, malic, tartaric, citric, ascorbic, maleic, hydroxymaleic, benzoic, hydroxy-benzoic, phenylacetic, cinnamic, salicylic, 2-phenoxy-benzoic, p-toluenesulfonic acid, and sulfonic acids such as methane sulfonic acid and 2-hydroxyethane sulfonic acid. Such salts can exist in either a hydrated or substantially anhydrous form.

The indole rings depicted in Formulae Ia and Ib are always substituted at positions 2 and 3, and may be optionally substituted at position 1. They may be further substituted as is indicated by the possible definitions for R. R may represent up to 3 additional substituents and these additional substituents may be located at any of positions 4, 5, 6, or 7. These substituents can be the same or different. In the compounds of Formulae Ia and Ib, R₁ and R₂ may be represented by the same substituents or differing substituents.

The compounds of Formula Ic exist as optical isomers. Any reference in this application to one of the compounds represented by Formula Ic is meant to encompass either a

specific optical isomer or a mixture of optical isomers (unless it is expressly excluded). The specific optical isomers can be separated and recovered by techniques known in the art such as chromatography on chiral stationary phases or resolution via chiral salt formation and subsequent separation by selective crystallization. Alternatively utilization of a specific optical isomer as the starting material will produce the corresponding isomer as the final product.

10 As is indicated by the E₂ substituent in the compounds of formula Id, the piperidine ring may be further substituted at positions 4, 5, or 6. E₂ may optionally represent up to 2 non-hydrogen substituents. Only one non-hydrogen substituent should be located at any one position
15 on the piperidine ring. If two non-hydrogen substituents are present, they may be the same or different. When E₂ is a non-hydrogen substituent, then this substituent may be either syn or anti relative to the phosphono substituent.

20 All of the compounds of Formula Id contain at least two (2) asymmetric centers and thus will exist as diastereoisomers. Any reference to these compounds as well as their intermediates should be construed as encompassing a racemic mixture, a specific optical isomer or a pair of enantiomers.
25 The specific optical isomers can be synthesized as shown herein or can be recovered by techniques known in the art such as chromatography on chiral stationary phases, or resolution via chiral salt formation and subsequent separation by selective crystallization. HPLC ion exchange
30 chromatography may be utilized to separate only the diastereoisomers.

Examination of Formula Id shows that the compounds

compounds will exist in a state of tautomeric equilibrium in which the carbonyl function will participate in a keto-enol equilibrium reaction.

5 The compounds of Formula Ia in which X is represented by S is known in the art. The synthesis of these compounds, their use as excitatory amino acid antagonists, and methods for preparing pharmaceutical compositions from them are described in United States Patent No. 5,051,442 which is
10 hereby incorporated by reference. The preferred compounds of the 442' patent are those in which R is represented by a 4,6-dihalo substituent, X is S, m is 1, and Z is H. The most preferred compound is 3-[(carboxymethyl)thio]-2-carboxy-4,6-dichloroindole.

15 Those compounds of Formula Ia in which X is a C₁₋₄ alkylene, and neither R₁ nor R₂ contain a heterocyclic ring are also known in the art. The use of the compounds as excitatory amino acid antagonists, and methods for preparing pharmaceutical compositions from them are described in
20 United States Patent No. 4,960,786 which is hereby incorporated by reference. The preferred compounds of the '786 patent are those in which R is represented by a 4,6-dihalo substituent, Z is H and X is ethylene. The most preferred compound is 3-(carboxyethyl)-2-carboxy-4,6-
25 dichloroindole.

30 Those compounds of Formula Ia in which X is a C₁₋₄ alkylene, and one of R₁ or R₂ contain a heterocyclic ring are the subject of United States Patent Application No. 742,146 filed August 1, 1991, having an effective filing date of July 16, 1990, now allowed, which is hereby incorporated by reference. This application discloses methods for
35 synthesizing these compounds, their use as excitatory amino

acid antagonists, and methods for preparing pharmaceutical formulations from them. Preferred compounds are those in which R is represented by a 4,6-dihalo substituent.

5 The compounds of Formula Ib are the subject of United States Patent Application No. 07/608,457, filed November 2, 1990, which is hereby incorporated by reference. This application describes methods for their synthesis, their use as excitatory amino acid antagonists and pharmaceutical
10 formulations containing them. Preferred compounds are those in which R is a 4,6-dihalo substituent, B is alkyl, Z is hydrogen and A is phenyl. The most preferred compound is 3-[(phenacyl)methylamino]-2-carboxy-4,6-dichloroindole.

15 The compounds of Formula Ic are known in the art and are described in European Patent Application No. 0 418 863 as well as its US counterpart, Patent Application No. 553,431 filed July 20, 1990, now allowed, which is hereby incorporated by reference. These applications describe
20 methods for their synthesis, their use as excitatory amino acid antagonists and pharmaceutical formulations containing them. Preferred compounds include those in which A is methylene and E and E₁ are hydrogen. The most preferred compound is R-4-Oxo-5-phosphononorvaline.

25 The compounds of Formula Id are the subject of United States Patent Application No. 525, 290 filed May 17, 1990 which is hereby incorporated by reference. This application discloses methods for their synthesis, their use as
30 excitatory amino acid antagonists and pharmaceutical formulations containing them. Preferred compounds include those in which the stereochemistry is 2R,3S and in which E₅ is hydrogen or 4-alkyl. Preferred compounds include 3-(phosphonoacetyl)piperidine-2-carboxylic acid and 3-

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Probenecid is also known in the art. It is available commercially from Merck Sharp and Dohme under the tradename Benemid[®] as well as being available from numerous other sources. Probenecid is a uricosuric agent and is utilized in the treatment of gout. Probenecid is a renal tubular transport blocking agent and has been utilized to increase plasma levels of penicillin. The pharmacology of probenecid is described in detail in the 45th Edition of the Physicians Desk Reference on page 1379.

10

As noted above, the compounds of Formulae Ia-Id are excitatory amino acid antagonists. They antagonize the effects which excitatory amino acids have upon the NMDA receptor complex. The compounds of Formula Ia and Ib preferentially bind to the strychnine-insensitive glycine binding site located on the NMDA receptor complex. The compounds of formula Ic and Id preferentially bind to the glutamate binding site located on the NMDA receptor complex. The compounds of formulae Ia-Id (hereinafter the compounds) are useful in the treatment of a number of disease states.

20

Ischemia, hypoglycemia, and trauma have been shown to raise extracellular concentrations of glutamate and aspartate to potentially neurotoxic levels. These antagonists will be neuroprotective in these and potentially other syndromes characterized by elevated glutamate and or aspartate concentrations. Thus the compounds are useful for preventing or minimizing the damage which nervous tissues contained within the CNS suffer upon exposure to either ischemic, hypoxic, traumatic or hypoglycemic conditions. Representative examples of such ischemic, hypoxic, or hypoglycemic conditions include strokes or cerebrovascular accidents, carbon monoxide poisoning, hyperinsulinemia, cardiac arrest, drownings, suffocation, reduction of neuronal damage following trauma to the brain or spinal

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cord, and neonatal anoxic trauma. The compounds should be administered to the patient within 24 hours of the onset of the hypoxic, ischemic, or hypoglycemic condition in order for the compounds to effectively minimize the CNS damage which the patient will experience.

The compounds exhibit anti-convulsant properties and are useful in the treatment of epilepsy. They are useful in the treatment of grand mal seizures, petit mal seizures, psychomotor seizures, and autonomic seizures. The compounds are also useful in the treatment of neurodegenerative diseases such as Huntington's disease, Alzheimer's disease, senile dementia, glutaric acidemia type I, multi-infarct dementia, and neuronal damage associated with uncontrolled seizures. The administration of these compounds to a patient experiencing such a condition will serve to either prevent the patient from experiencing further neurodegeneration or it will decrease the rate at which the neurodegeneration occurs. As is apparent to those skilled in the art, the compounds will not correct any CNS damage that has already occurred as the result of either disease or a lack of oxygen or sugar. As used in this application, the term "treat" refers to the ability of the compounds to prevent further damage or delay the rate at which any further damage occurs. The compounds may also be utilized as anxiolytic agents and as analgesics. The therapeutic activity of these compounds is described in more detail in the United States patents and patent applications which were incorporated by reference above.

The compounds may be administered concurrently with probenecid in order to treat any of the diseases or conditions described above. The quantity of probenecid that

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compound of Formulae Ia-d being administered, the patient, and the presence of other underlying disease states within the patient, etc. Typically though, the probenecid may be administered at a dosage of from 0.5-3g/day. Repetitive
5 daily administration may be desirable and will vary according to the conditions outlined above. The probenecid will typically be administered from 2-4 times daily.

The dosage range at which the compounds of Formulae
10 Ia-d exhibit their effects can vary widely depending upon the particular disease being treated, the severity of the patient's disease, the patient, the particular compound being administered, the route of administration, and the
15 patient, etc. The dosage range at which the compounds of Formula Ia-d exhibit their antagonistic effect is presented below in Table I.

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Table I

COMPOUNDS	DOSAGE RANGE (Mg/Kg-day)
Ia	0.1 - 50
Ib	0.1 - 50
Ic	1 - 500
Id	0.1 - 500

With the concurrent administration of probenecid, this dosage range may be adjusted lower by a factor of from 2- to 10-fold. Alternatively, the compounds may be administered at the same dosage range in order to obtain an enhanced effect due to the higher therapeutic concentrations obtained. The dosage frequency of the compounds can vary widely depending upon the condition or disease being treated. Repetitive daily administration may be desirable and will vary according to the conditions outlined above. For certain conditions such as stroke, it may be desirable to maintain a continuous IV infusion.

Probenecid is currently available commercially as tablets. The sodium salt of probenecid is readily water soluble and injectable dosage forms can be prepared from this salt using techniques well known to those skilled in the art.

The compounds may be administered by a variety of routes. They are effective if administered orally. The compounds may also be administered parenterally (i.e. intravenously, intravenously, intramuscularly,

patents and patent applications discussed above teach methods for preparing pharmaceutical dosage forms containing the compounds.

5 The compounds of Formulae Ia-d and the probenecid may be administered as two different pharmaceutical dosage forms. Alternatively, in order to increase patient convenience, the compounds and the probenecid may be compounded into a single pharmaceutical dosage form. These pharmaceutical
10 compositions can be manufactured utilizing techniques known in the art. Typically an antagonistic amount of the compound and an effective amount of probenecid will be admixed with a pharmaceutically acceptable carrier.

15 For oral administration, the two medicaments can be formulated into solid or liquid preparations such as capsules, pills, tablets, lozenges, melts, powders, suspensions, or emulsions. Solid unit dosage forms can be capsules of the ordinary gelatin type containing, for
20 example, surfactants, lubricants and inert fillers such as lactose, sucrose, and cornstarch or they can be sustained release preparations. In another embodiment, the two medicaments can be tableted with conventional tablet bases such as lactose, sucrose, and cornstarch in combination with
25 binders, such as acacia, cornstarch, or gelatin, disintegrating agents such as potato starch or alginic acid, and a lubricant such as stearic acid or magnesium stearate. Liquid preparations are prepared by dissolving the active ingredients in an aqueous or non-aqueous pharmaceutically
30 acceptable solvent which may also contain suspending agents, sweetening agents, flavoring agents, and preservative agents as are known in the art.

For parenteral administration the two medicaments may be
35 dissolved in a physiologically acceptable pharmaceutical

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carrier and administered as either a solution or a suspension. Illustrative of suitable pharmaceutical carriers are water, saline, dextrose solutions, fructose solutions, ethanol, or oils of animal, vegetative, or
5 synthetic origin. The pharmaceutical carrier may also contain preservatives, buffers, etc., as are known in the art. When the medicaments are being administered intrathecally, they may also be dissolved in cerebrospinal fluid as is known in the art.

10

As used in this application:

a) the term "patient" refers to warm blooded animals such as, for example, guinea pigs, mice, rats, cats, rabbits,
15 dogs, monkeys, chimpanzees, and humans;

b) the term "treat" refers to the ability of the compounds to either relieve, alleviate, or slow the progression of the patient's disease;

20

c) the term "neurodegeneration" refers to a progressive death and disappearance of a population of nerve cells occurring in a manner characteristic of a particular disease state and leading to brain damage;

25

d) the phrase "concurrent administration" refers to administering the probenecid at an appropriate time so that it will potentiate the antagonistic effects of the compounds of Formula I. This may mean simultaneous administration or
30 administration at appropriate but different times. Establishing such a proper dosing schedule will be readily apparent to one skilled in the art.

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construed as limiting the scope of the invention in any manner.

EXAMPLE I

5

One method for evaluating the potential anti-epileptic activity of selected compounds is by their ability to inhibit sound induced seizures in audiogenic mice. DBA/2J audiogenic mice experience seizures when exposed to loud noises. Compounds which prevent this phenomenon are considered to be antiepileptic agents.

Groups of 4 to 8 DBA/2J audiogenic mice were administered i.p. 4 to 5 doses ranging from 25 to 400 mg/kg of 3-[(phenacyl)methylamino]-2-carboxy-4,6-dichloroindole (hereinafter compound). Two hours after administration, they were placed individually in glass jars and exposed to a sound stimulus of 110 decibels for 30 seconds. Each mouse was observed during the sound exposure for signs of seizure activity. A graph was prepared based upon the dose administered and the percentage of animals protected at that dose. An ED₅₀ was calculated from the graph. In some mice the test was performed with the only modification being the addition of 100mg/kg of probenecid IP. The following ED₅₀'s were obtained.

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TREATMENT	ED ₅₀ (mg/kg)
Compound	183.7
Compound + Probenecid	45.4

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B) The protocol described above was repeated with minor variations with the compound 3-[(carbethoxymethyl)thio]-2-carbethoxy-4,6-dichloroindole. The test was conducted in the following manner.

Groups of DBA/2J audiogenic mice were administered i.p. 6 doses ranging from 25 to 400 mg/kg of 3-[(carboxymethyl)thio]-2-carboxy-4,6-dichloroindole (hereinafter compound). Five minutes after administration, they were placed individually in glass jars and exposed to a sound stimulus of 110 decibels for 30 seconds. Each mouse was observed during the sound exposure for signs of seizure activity. A graph was prepared based upon the dose administered and the percentage of animals protected at that dose. An ED₅₀ was calculated from the graph. The test was also performed in separate mice with the only modification being the addition of 100mg/kg or 200mg/kg of probenecid IP. The following ED₅₀'s were obtained.

TREATMENT	ED ₅₀ (mg/kg)
Compound	149
Compound + 100 mg/kg probenecid	45.2
Compound + 200 mg/kg	11.0

EXAMPLE II

The intracerebroventricular administration of quinolinic acid induces clonic seizures in mice. If a compound can prevent or reduce these seizures, it is considered

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demonstrates the manner in which probenecid potentiated the ability of R-4-Oxo-5-phosphononorvaline to inhibit the development of these seizures.

5 In this test, groups of 10 mice were pretreated intravenously with varying doses of R-4-Oxo-5-phosphononorvaline(hereinafter compound) ranging from 1 to 16 mg/kg. Five minutes later the mice were administered 7.7 micrograms of quinolinic acid intracerebroventricularly in a
10 volume of 5 microliters of saline. The animals were observed for 15 minutes thereafter for signs of clonic seizures. A graph was prepared based upon the dose administered and the percentage of animals protected at that dose. An ED₅₀ was calculated from the graph. The test was
15 then repeated in separate mice with the only modification being the addition of 100mg/kg of probenecid IP. The following ED₅₀'s were obtained.

20

TREATMENT	ED ₅₀ (mg/kg)
Compound	4.0
Compound + Probenecid	2.3

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The protocol described above was repeated except that the compounds was administered intraperitoneally (dosage ranging from 0.5 to 32 mg/kg) and the pretreatment time was extended to 30 minutes. The following ED₅₀'s were obtained.

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TREATMENT	ED ₅₀ (mg/kg)
Compound	16.3
Compound + Probenecid	8.0

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WHAT IS CLAIMED IS:

10 1. A pharmaceutical composition suitable for
antagonizing the effects of excitatory amino acids upon the
NMDA receptor complex comprising an effective amount of
probenecid and an antagonistic amount of a compound of the
formulae:

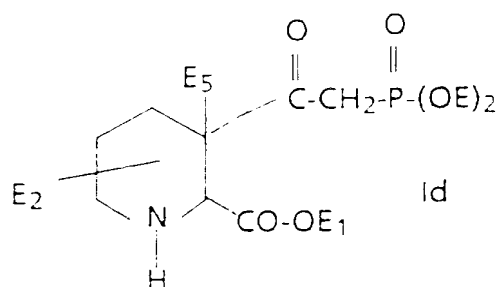
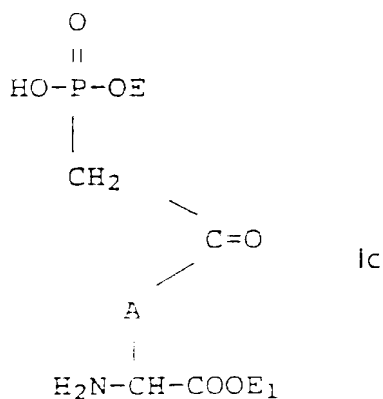
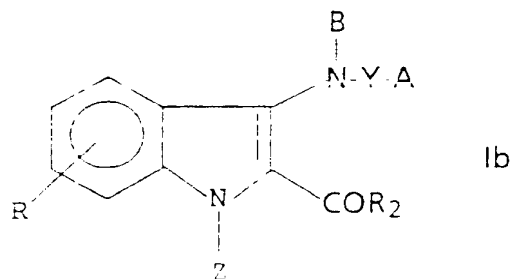
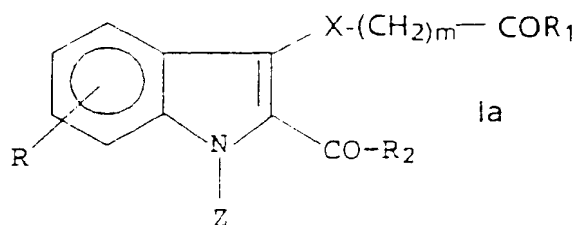
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35 a) in the compounds of Formula Ia, X is represented by a C₁₋₄ alkylene, or S; m is an integer from 1-4; Z is represented

- by H, C₁₋₄ alkyl, phenyl, substituted phenyl, or an alkylphenyl substituent in which the phenyl ring may be optionally substituted; R is represented by hydrogen, halogen, C₁₋₄ alkyl, C₁₋₄ alkoxy, CF₃, OCF₃, OH, NO₂, or CN;
- 5 R₁ and R₂ are each independently represented by -OH, -OR₃, -NR₄R₅, -OCH₂OR₃, or -O-(CH₂)_n-NR₆R₇, in which n is an integer from 1-4; R₃ is represented by C₁₋₄ alkyl, phenyl, substituted phenyl or an alkylphenyl substituent in which the phenyl ring may be optionally substituted; R₄ and R₅ are
- 10 each independently represented by hydrogen or a C₁₋₄ alkyl; R₆ and R₇ are each independently represented by hydrogen or a C₁₋₄ alkyl, or R₆ and R₇ together with the adjacent nitrogen atom form a piperidino, morpholino, or pyrrolidino group; with the proviso that if X is a C₁₋₄ alkylene, then m is 0;
- 15
- b) in the compounds of Formula Ib, R, Z, and R₂ are as above, B is represented by hydrogen, C_{1-C4} alkyl, optionally substituted alkylphenyl, or -CH₂-COR₂; Y is SO₂ or CO; A is represented by phenyl, substituted phenyl, or C(O)D in which D is defined as R₂ above;
- 20
- c) in the compounds of Formula Ic, E is represented by hydrogen, C₁₋₄ alkyl, or -CF₃; A is represented by a methylene or a trimethylene bridging group; and E₁ is
- 25 represented by hydrogen, C₁₋₄ alkyl, cycloalkyl, trialkylamino, alkylphenyl, phenyl, or substituted phenyl;
- d) in the compounds of Formula Id E and E₁ are as above, E₂ is represented by hydrogen, C_{1-C4} alkyl, phenyl, alkylphenyl,
- 30 or cyclohexylmethyl;
- E₃ is represented by hydrogen, linear C_{1-C4} alkyl, or alkylphenyl; or a pharmaceutically acceptable salt of any of the compounds of Formulae Ia-d, in admixture with a

2. Use of a composition according to claim 1 as a medicament for the treatment of epilepsy.

3. Use of a composition according to claim 1 as a medicament for the treatment of neurodegenerative diseases.

4. Use of a composition according to claim 1 as a medicament for preventing ischemic/hypoxic damage to cerebral tissue.

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5. Use of a composition according to claim 1 as a medicament for the treatment of anxiety.

6. Use of a composition according to claim 1 as a medicament for producing an analgesic effect.

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A. CLASSIFICATION OF SUBJECT MATTER

IPC5: A61K 31/19, A61K 31/405, A61K 31/445, A61K 31/66
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC5: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CA, MEDLINE, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	GB, A, 2100127 (SANTEN PHARMACEUTICAL CO LTD), 22 December 1982 (22.12.82), page 1, line 7 - line 17	1-6
Y	US, A, 4960786 (F G SALITURO ET AL), 2 October 1990 (02.10.90)	1-6
Y	US, A, 5051442 (F G SALITURO ET AL), 24 Sept 1991 (24.09.91)	1-6

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

- * Special categories of cited documents
- * "A" document defining the general state of the art which is not considered to be of particular relevance
- * "E" earlier document but published on or after the international filing date
- * "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- * "O" document referring to an oral disclosure, use, exhibition or other means
- * "P" document published prior to the international filing date but later than the priority date claimed

- * "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- * "X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- * "Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- * "Z" document member of the same patent family

Date of mailing of the international search report

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INTERNATIONAL SEARCH REPORT

international application No.

PCT/US 92/10354

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	Brain Research Bulletin, Volume 28, 1992, Laszlo Vécsei et al, "Kynurenine and Probenecid Inhibit Pentylenetetrazol- and NMDLA-Induced Seizures and Increase Kynurenic Acid Concentrations in the Brain", page 233 - page 238, abstract --	1-6
P,X	WO, A1, 9215565 (MERRELL DOW PHARMACEUTICALS INC.), 17 Sept 1992 (17.09.92), page 13 -- -----	1-6

INTERNATIONAL SEARCH REPORT

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29/01/93

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Patent document cited in search report		Publication date	Patent family member(s)		Publication date
GB-A-	2100127	22/12/82	BE-A-	890398	18/01/82
			DE-T-	3152363	21/11/85
			FR-A,B-	2490490	26/03/82
			JP-C-	1406415	27/10/87
			JP-A-	57056425	05/04/82
			JP-B-	62013923	30/03/87
			SE-A-	8203054	14/05/82
			US-A-	4424228	03/01/84
			WO-A-	8200954	01/04/82
US-A-	4960786	02/10/90	AU-B-	625998	23/07/92
			AU-A-	5378090	25/10/90
			EP-A-	0394905	31/10/90
			JP-A-	2295924	06/12/90
US-A-	5051442	24/09/91	AU-A-	7650091	11/11/91
			WO-A-	9116307	31/10/91
WO-A1-	9215565	17/09/92	AU-A-	1532092	06/10/92



PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PHM 70471/WO	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/GB00/00260	International filing date (day/month/year) 31/01/2000	Priority date (day/month/year) 05/02/1999
International Patent Classification (IPC) or national classification and IPC C07D209/42		
Applicant ASTRAZENECA AB et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

- ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability, citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☒ Certain defects in the international application
- VIII ☒ Certain observations on the international application





INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB00/00260

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):
- Description, pages:**

1-39 as originally filed

Claims, No.:

1-10 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, pages:



INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB00/00260

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-10
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-10
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-9
	No:	Claims	10 see below

2. Citations and explanations
see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet



**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB00/00260

V. CITATIONS AND EXPLANATIONS

The following documents are mentioned in this report.

US-A-5,288,743	(A)
WO-A-99 33800	(B)
WO-A-99 07678	(C)
WO-A-99 07351	(D)

The novel feature of the indole derivative of claim 1 is the R4 group, representing an acylamino, sulfonylamino or aminocarbonyloxy group, present at the 4-position of the ring. The dependent claims 2-7, as well as claim 8 drawn to a process for the preparation of compounds of claim 1, and claims 9 and 10 drawn to pharmaceutical compositions containing compounds of claim 1 and compounds of claim 1 for use in the preparation of medicaments are novel by consequence. Claims 1 to 10 therefore meet the Novelty requirements of Article 33(2) PCT.

Document (A) represents the closest prior art. This document describes some 1-benzyl-2-carboxyalkyl-5-(heterocyclylmethoxy)-indoles and their use for the inhibition of leukotriene synthesis. the compounds of document (A) are useful for the treatment of inflammation (see column 2, lines 15-20). The presently claimed compounds also have anti-inflammation activity, and differ from the compounds of document (A) through the absence of an alkyl group linking the carboxy group to the 2-position. and through the presence of the R4 group as defined above at the 4-position of the indole ring. Hence the presently claimed compounds are not structurally close to the compounds of document (A), and it would not have been obvious for the skilled man to prepare them in order to make available further anti-inflammation compounds. Inventive step (Article 33(3) PCT) is recognise because the problem of providing further anti-inflammation compounds has been solved in a non obvious manner.

For the assessment of the present claim 10 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can



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**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB00/00260

for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

At present no priority document is available. The examination has been carried out assuming that the priority date is validly claimed. If during the subsequent procedure (e.g. EPO examination) the priority date is found to be invalid for some or all of the presently claimed subject matter, the intermediate documents (B)-(D) may be taken into consideration for the evaluation of Novelty and inventive step.

VII CERTAIN DEFECTS IN THE INTERNATIONAL APPLICATION.

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents (A) and (B) is not mentioned in the description, nor are these documents identified therein.

VIII. CERTAIN OBSERVATIONS ON THE INTERNATIONAL APPLICATION.

Claim 1 contains several non-limiting definitions such as "optionally substituted aryl" and "optionally substituted heteroaryl", etc. which embrace substitution by any known organic group without limitation on size or number of reactive groups which can be present. The term "heteroaryl" itself embraces any known aromatic heterocyclic group. It is known in pharmaceutical chemistry that small structural changes to heterocyclic rings can lead to considerable changes in a pharmacological activity, or to compounds with a completely different activity. The skilled man would therefore not be able to predict if all compounds falling within the said definition "heteroaryl" would actually solve the problem underlying the present application (i.e. the provision of MCP-1 inhibitors). Also, since the term "functional group" appears to embrace any reactive group and is not limited to the groups suggested on page 4, lines 10-14, it is not clear if the presence of any "functional group" at R4-R7 would give rise to a compound which binds to a MCP-1 receptor, because some reactive groups would be expected to react at competing binding sites.



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